JACC Vol. 29, No. 6
May 1997:1284–9

Timing of First Recurrence of Syncope Predicts Syncopal Frequency After a Positive Tilt Table Test Result

PAUL MALIK, MD, MARY LOU KOSHMAN, RN, ROBERT SHELDON, MD, PHD

Calgary, Alberta, Canada

Objectives. **This study sought to determine whether the time to first recurrence of syncope after a positive isoproterenol–tilt table test result accurately predicts the eventual frequency of syncope.**

Background. **Both patient care and future clinical trials involving patients with neuromediated syncope will require a simple measure that reflects the frequency of syncope. The time from tilt table testing to the first recurrence of syncope might be such a measure.**

Methods. **A cohort of 46 patients with syncope, in a university outpatient clinic, who had at least one syncopal spell after a positive isoproterenol–tilt table test result were followed up for up to 6.5 years (mean [±SD] 48 ± 14 months). The time from tilt table testing to the first recurrence of syncope was correlated.**

Results. **A total of 40 of 46 patients had more than one recurrent spell, with a median of eight recurrent spells. The time to the first syncopal spell predicted the frequency of spells with $r = -0.79$ ($p < 0.001$), whereas the time to the second spell predicted the frequency with $r = -0.92$ ($p < 0.001$). Patients who fainted within 1 month of tilt testing had a geometric mean frequency of 1.35 spells/month (95% confidence limits 0.49, 3.74) compared with patients who fainted 1 to 24 months after testing (0.12 spells/month; 95% confidence limits 0.07 to 0.18, $p < 0.001$). Finally, the frequency of syncopal spells bore no relation to the duration of follow-up.**

Conclusions. **The time to the first recurrent spell predicts the frequency of syncopal spells after a positive tilt table test result, and the instantaneous risk of syncope is constant.**

(J Am Coll Cardiol 1997;29:1284–9)

Numerous studies with head-up tilt table testing have shown that many patients with recurrent syncope have a syndrome of neuromediated syncope. Interest is now turning to studies of the outcome of this syndrome, partly to assist in patient counseling and partly to help design clinical trials of therapeutic interventions. Recently, we identified several clinical risk factors that could be used to predict an early recurrence of a syncopal spell after a positive tilt table test result (1). Factors that predicted the time to first recurrence of syncope included the number of historical syncopal spells, the duration of syncopal symptoms, the frequency of syncopal spells and several tilt test variables. Syncope was chosen as the primary symptom because it was memorable and easily quantifiable and because apprehension of syncope appears to be the main cause of decreased quality of life in syncopal patients (2,3). The time to first recurrence of syncope was chosen as the primary end point because Pritchett and colleagues (4–6) had validated the time to the first recurrence of arrhythmia as an accurate measure of frequency of recurrences in atrial fibrillation and supraventricular tachycardia.

However, the use of this multivariate predictive model has potential drawbacks. It demands a reasonably accurate assessment of the duration and frequency of historical syncopal spells and is partly based on a specific tilt test protocol that involved the use of high dose isoproterenol. Furthermore, many patients have a marked decrease in their symptoms after tilt testing (1,7). For these reasons we wished to develop a simple, practical measure of the eventual frequency of syncope after tilt table testing. In light of the proven usefulness of first recurrence time in other paroxysmal disorders, it seemed reasonable to attempt to validate the time to first recurrence of syncope after tilt testing as an outcome measure in the syndrome of neuromediated syncope.

This study had two purposes: 1) We wished to determine whether the time to the first recurrence of syncope after a positive tilt table test result predicts the frequency of syncope during the long-term follow-up period; and 2) we wished to determine whether the frequency of syncope was idiosyncratic and constant for each patient, as would be expected for a random process with idiosyncratic instantaneous relative risks.

Methods

Inclusion and exclusion criteria. Patients underwent tilt table testing if they had had 1) two or more syncopal episodes; or 2) one syncopal episode and four or more presyncopal

From the Cardiovascular Research Group, University of Calgary, Calgary, Alberta, Canada. This study was supported by grants from the Medical Research Council of Canada (PG11188), Ottawa and the Calgary General Hospital Research and Development Committee, Calgary, Canada.

Manuscript received October 25, 1996; revised manuscript received January 24, 1997, accepted January 30, 1997.

Address for correspondence: Dr. Robert Sheldon, Department of Medicine, University of Calgary, Health Sciences Center, 3330 Hospital Drive NW, Calgary, Alberta, Canada T2N 4N1.

0735-1097/97/$17.00
PII S0735-1097(97)00047-8

episodes; or 3) a single episode of syncope causing serious injury (1). Patients were eligible for this study if they were followed up for at least 24 months after a positive isoproterenol–tilt table test result and had at least one syncopal spell after the tilt test. The 24-month period was selected as a reasonably long period of observation, and by definition patients had to have had at least one recurrence of syncope to qualify for the study. Patients with other causes of syncope were excluded from the study. In particular, patients with structural heart disease, documented ventricular tachycardia or bifascicular block also underwent ambulatory electrocardiography and programmed electrical stimulation using a previously described protocol (8). In the global patient cohort (n = 338), which included patients with other causes of syncope, 196 had a positive tilt table test result. Of these 196, 33 patients were lost to follow-up. The remaining 163 patients constitute the parent cohort of the subjects of this report. The baseline clinical characteristics and tilt test variables of the patients lost to follow-up closely resemble the characteristics of the parent cohort (1).

Tilt table test. Patients underwent tilt table testing (9–11) in a quiet room after they had fasted for 4 to 8 h. No patient underwent tilt table testing while taking beta-adrenoceptor blocking agents (9), disopyramide or drugs with anticholinergic activity. They were comfortably restrained on an electric tilt table. Instrumentation consisted of a peripheral intravenous cannula and automatic and manual blood pressure cuffs. The test ended after frank syncope during an infusion of 5 μg/min of isoproterenol or after 10 min in the head-up position with either presyncope or no symptoms. Heart rate, blood pressure and symptoms were recorded each minute. Tilt test results were deemed *positive* if they ended in syncope or presyncope and a decrease in rate–pressure product to ≤9,000 mm Hg/min (10).

Definitions. *Duration of symptoms* = number of months elapsed between the first historical syncopal spell and the diagnostic tilt table test; *observation period* = duration of follow-up after the tilt table test; *frequency of syncope* = numerical ratio of the number of spells divided by the duration of symptoms.

Interventions and follow-up. After tilt testing and a rest period, all patients underwent counseling regarding the diagnosis, possible pathophysiology, lack of mortality and uncertain symptomatic prognosis of neuromediated syncope. All patients were reassured, counseled on recognizing their presyncopal prodromal symptoms and urged to take specific appropriate postural maneuvers when presyncopal. Throughout this study we recognized the lack of Phase I to IV studies (12) demonstrating drug efficacy. This was discussed, and no patient was urged to accept empiric drug therapy. All patients who started drug therapy did so at their own request. We used beta-blockers (when not contraindicated) for initial treatment (9). All patients were asked to notify the syncope clinic of their first recurrence, and all were contacted at least every 6 months by telephone.

Statistical analysis. The primary outcome measure was the frequency of syncopal spells during follow-up, calculated as the number of spells divided by the duration of the observation period. Patients with large numbers of syncopal spells (usually >10) were asked to estimate the frequency of syncopal spells in demarcated epochs of follow-up. This frequency was then converted to an estimate of the number of spells, which was confirmed by the patient. Although this is accurate for patients with few spells, some error can be expected with patients with many spells. Dependent variables included the time from tilt testing to the first recurrence, the time between the first and second recurrences after tilt testing and the time from tilt testing to the second recurrence.

We first determined whether the variable was normally distributed or skewed. The skewed distributions were analyzed after logarithmic transformation, and the data are presented as geometric mean ± 95% confidence limits. Mean values (±SD) and medians were calculated for continuous variables, and frequencies were measured for categoric variables. Differences between groups were examined for statistical significance by a two-sample *t* test for continuous variables (using a logarithmic transformation on skewed distributions where appropriate) and by the Fisher exact test for categoric variables. Linear regression was performed on appropriately transformed data. Although the duration of observation was normally distributed, the number and frequency of recurrent syncopal spells were log distributed. Accordingly, the data analysis was performed using in large part log-transformed data, which were normally distributed with 80% confidence as assessed by the Kolmogorov-Smirnov test. Because the primary hypothesis is that the time to first spell is a reciprocal function of the frequency of spells (as are heart periods the reciprocal of heart rate), each relation takes the reciprocal form $y = ax^b$, where y is the observed frequency, and x is the time to first syncope recurrence. Because the constants a and b were derived from log-normalized data, they are expressed as mean values and 95% confidence intervals.

Results

Study patients. A total of 46 patients had at least one syncopal spell within the first 2 years after a positive tilt test result (34 women, 12 men; mean age 32 ± 17 years). They had had a median of 17 spells (mean 223 ± 916) over a median of 36 months (mean 68 ± 79). They had a median frequency of 0.47 spells/month (mean 6 ± 25) before tilt table testing. During the tilt table test, 28 patients developed syncope, and 18 developed presyncope only.

Medication use during study period. No patient was taking medication for prevention of syncope at the time of tilt table testing. However, it was impossible to maintain most patients in the drug-free state throughout the study. Most patients (n = 35) at some point sought and received empiric attempts at medical therapy. After the tilt test, 23 patients were started on beta-blocking agent therapy, 3 received other drugs, and 20 were not treated. After the first syncopal recurrence, 28 patients received beta-blockers, 2 received other drugs, and 16 were not treated. After the first recurrence of syncope, 15

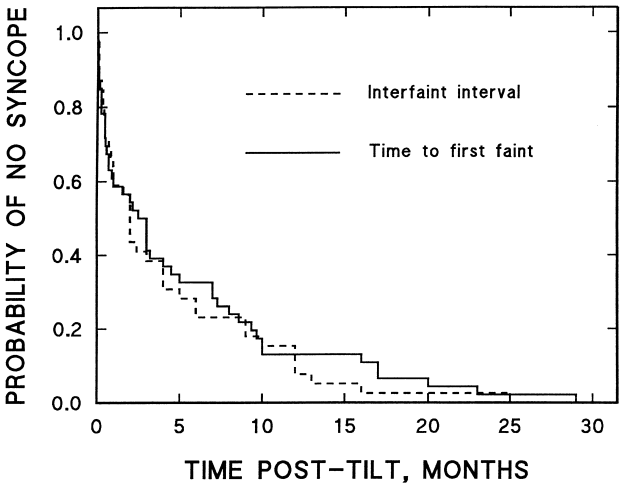

Figure 1. Actuarial probabilities of remaining free of syncope after a positive tilt test result in 46 patients who had at least one spell after a positive tilt test (**solid line**), and in 40 patients who fainted after their first recurrent spell (**dashed line**).

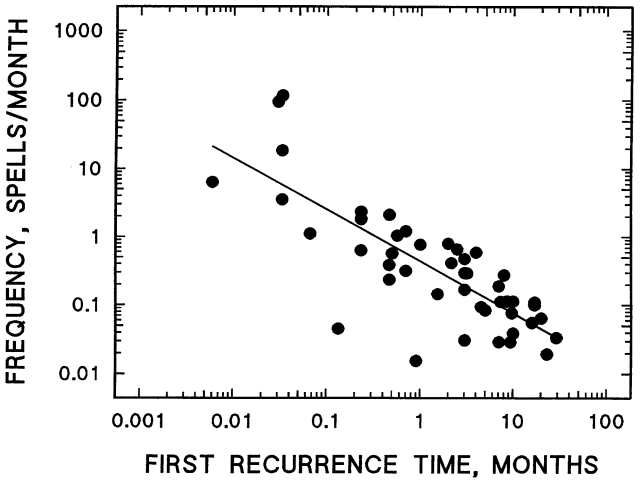

Figure 2. First recurrence times and eventual frequency of syncope. The relation is Observed frequency = 0.44(Time to first recurrence)$^{-0.77}$, with r = −0.79, p < 0.001. The confidence limits of the exponent are −0.58, −0.94.

patients had a change in the intention to treat (or not treat) their syncope.

Recurrence characteristics. The patients were observed for 44 ± 18 months (range 24 to 80), which included the time from the tilt test to the first syncopal spell. The total cohort had a median of 8 recurrent syncopal spells (mean 241 ± 969) with a median posttest frequency of 0.28 spells/month (mean 6 ± 22), and 40 of 46 patients had more than 1 recurrent spell. Syncope recurred quickly after tilt testing (Fig. 1), with a median time to first recurrence of 2.75 months (mean 5.3 ± 6.9) and a median time between the first and second syncopal spells of 2.0 months (4.4 ± 5.6). The median time from the tilt test to the second recurrence was 4.2 months (mean 8.8 ± 9.7).

Eventual syncopal frequency and recurrence times. Figure 2 shows that log(Observed frequency) and log(Time to first spell) correlate well (r = −0.79, p < 0.001), according to the relation Observed frequency = 0.44(First recurrence time)$^{-0.7}$. To determine whether the risk of syncope in each patient changes over time, we assessed the relation between the frequency of syncopal spells/patient as a function of the length of follow-up. There was no correlation (r = −0.03), in keeping the concept that the risk of syncope for each patient does not decline with time.

If each syncopal spell reflects a single observation in a recurrent process, then increasing the number of observations should allow a more precise estimate of the nature of the process. To test this hypothesis, we correlated the time from tilt test to the second recurrence of syncope with the final observed frequency of syncope. Figure 3 shows that log(Observed frequency) and log(Time to second spell) correlate well (r = −0.92, p < 0.001), according to the relation Observed frequency = 1.54 (First recurrence time)$^{-1.0}$. Similarly, the interval between syncopal spells should be a function of the reciprocal of the overall syncopal frequency. Figure 3 also shows that log(Interval between first and second spells) and log(Observed frequency) correlate well (r = −0.85, p < 0.001), according to the relation Observed frequency = 0.65(Intersyncope interval)$^{-0.91}$. In conclusion, syncope appeared to recur with an idiosyncratic and constant frequency during the observation period.

Dichotomous values and eventual syncope burden. Although smoothly continuous functions are helpful in predicting the expected syncopal frequency in individual patients, they are less helpful in designing clinical trials where entry criteria require dichotomous values to guide patient enrollment. Accordingly, we calculated the average frequencies of syncope in patients depending on whether they fainted within specified times after tilt testing. These estimates are presented in Table 1. For example, patients with a first recurrence within 1 month have a geometric mean syncope frequency of 1.35 spells/month, whereas patients with a recurrence time >1 month have a geometric mean syncope frequency of 0.12 spells/month (p < 0.001).

Subgroup analyses. Four subgroup analyses were performed to assess the robustness of the conclusions. First, we compared the relations between the time to the first recurrence of syncope in 11 patients who were never treated pharmacologically for syncope with those relations in 35 patients who were treated at some time during their clinical course after tilt testing. The data in Figure 4 show the similarity between these two groups; their relations are described in Table 2. Similarly, we compared these relations in patients who were or were not treated with beta-blockers at some time between tilt testing and the first syncopal recurrence; in patients who were or were not treated with beta-blockers after the first syncopal recurrence; and in patients whose intent to be treated was changed or unchanged after the first syncopal recurrence. The data (Table 2) show the great similarity in the constants in all groups. All confidence intervals overlapped, suggesting that

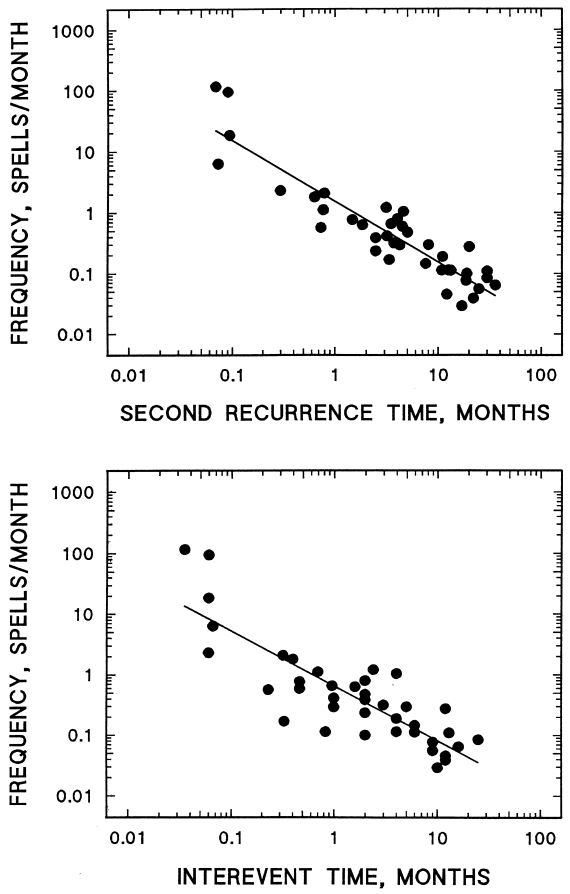

Figure 3. Top panel, Second recurrence times and eventual frequency of syncope. The relation is Observed frequency = 1.54(Time to second spell)$^{-1}$. The confidence limits of the exponent are −0.85, −1.14. **Bottom panel,** Interevent intervals and eventual frequency of syncope. The relation is Observed frequency = 0.65(Interval between first and second spells)$^{-0.91}$. The confidence limits of the exponent are −0.72, −1.10.

treatment had no effect on the relation between time to first syncopal recurrence and eventual frequency of syncope.

Discussion

The present study demonstrates that the time to first syncope recurrence is a simple, accurate method of predicting the future frequency of syncope in patients with neuromediated syncope. The eventual frequency of syncope closely correlates with a number of measures of the time between syncopal spells, including the time between the first and second recurrences, the time to first recurrence and the time to second recurrence. The exponents are close to −1, the expected value of a simple reciprocal relation. The best predictor of long-term outcome is time to second spell (r = −0.92). This increased correlation coefficient may be due to the fact that this measure samples two intervals—the time to first recurrence and the time between first and second recurrences—and therefore is more influenced by the true recurrence rate and less by the sampling error of a single event.

Table 1. Relation of Observed Frequency of Syncopal Spells After Tilt Test to Time to First Syncopal Spell After Tilt*

		Observed Frequency of Syncopal Spells/mo	
First Syncope	No. of Pts	Mean ± SD	Geometric Mean (95% CL)
In ≤2 wk	14	18 ± 38	2.2 (0.68, 7.17)
In >2 wk	32	0.27 ± 0.32	0.14 (0.09, 0.22)
In ≤1 mo	19	13 ± 33	1.35 (0.49, 3.74)
In >1 mo	27	0.20 ± 0.21	0.12 (0.08, 0.18)
In ≤3 mo	27	9.5 ± 28	0.84 (0.38, 1.86)
In 3–24 mo	19	0.13 ± 0.14	0.09 (0.06, 0.13)
In ≤6 mo	32	8.3 ± 26	0.69 (0.34, 1.42)
In >6 mo	14	0.09 ± 0.07	0.07 (0.05, 0.11)
In ≤1 yr	40	6.4 ± 23	0.43 (0.23, 0.81)
In >1 yr	6	0.06 ± 0.04	0.05 (0.03, 0.09)

*Patients (Pts) were classified according to whether they fainted before or after the specified dichotomous times of 2 weeks and 1, 3, 6 and 12 months. All differences within pairs were significant at $p < 0.001$ for geometric means, and $p = 0.047$ to 0.053 for arithmetic means. CL = confidence limits.

We previously reported (1) a multivariate model of the effect of risk factors on the time to the first recurrence of syncope. The total number of historical syncopal spells, the duration of symptoms and the frequency of spells were each independent risk factors that predicted the time to first recurrence of syncope. This work validates the choice of time to first syncope recurrence by demonstrating that it correlates well with the eventual frequency of spells.

Choice of syncope as outcome measure. Outcome measures in studies of neuromediated syncope might include syncope; combined recurrences of presyncope and syncope; and quality of life (2,3). Syncope was chosen (1) because it is easily quantifiable and memorable. Presyncope was not chosen because of anticipated difficulties with its variable severity and duration. Indeed, recurrent presyncope is likely to be a significant problem in the lives of these patients.

Figure 4. First recurrence times and frequency of syncope in patients who never received or ever received drug treatment after tilt testing.

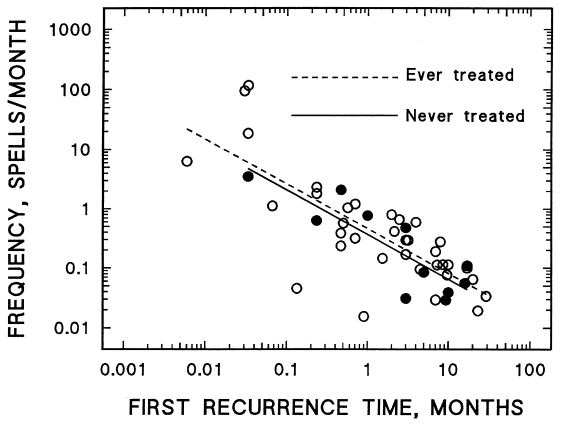

Table 2. Relation Between Time to First Recurrence of Syncope and Observed Frequency of Syncopal Spells in Selected Subgroups*

	No. of Pts	r Coeff	Slope	Exponent
Ever treated	35	−0.77	0.46 (0.29, 0.75)	−0.76 (−0.98, −0.53)
Never treated	11	−0.86	0.37 (0.18, 0.73)	−0.75 (−1.1, −0.41)
Beta-blockers after tilt test	23	−0.71	0.38 (0.20, 0.73)	−0.67 (−0.96, −0.37)
Drug free after tilt test	20	−0.84	0.44 (0.26, 0.75)	−0.82 (−1.1, −0.55)
Beta-blockers after 1st faint	28	−0.76	0.41 (0.26, 0.66)	−0.67 (−0.90, −0.44)
Drug free after 1st faint	16	−0.78	0.38 (0.18, 0.79)	−0.74 (−1.1, −0.41)
Change in intention to treat	15	−0.82	0.48 (0.21, 0.91)	−0.75 (−1.21, 0.29)
No change in intention to treat	31	−0.70	0.42 (0.27, 0.66)	−0.76 (−0.96, −0.56)
Total cohort	46	−0.79	0.44 (0.33, 0.64)	−0.76 (−0.94, −0.58)

*Subgroups are described in the Results section. Slope and exponent refer to the constants a and b, respectively, in the relation Syncopal frequency = a(Time to recurrence)^b. The value for a simple reciprocal relation is −1. Because the constants a and b were derived from log-normalized data, their values are expressed as mean value (95% confidence limits). Change in intention to treat refers to clinical decisions after the first recurrent faint. Coeff = coefficient.

Probability of syncopal recurrence during follow-up. The risk of syncope for each patient changes little during the follow-up period. This contrasts with our previous report that the probability of a first syncopal event in the cohort decreases after a positive tilt test result (1). The most likely explanation is that many patients learn early after assessment to abort the progression of presyncope to syncope, thus reducing the overall risk of syncope in the cohort. In contrast, patients who cannot act on their presyncopal prodrome will go on fainting.

Patients with syncope occasionally appear to have clusters of events over time. This study does not address this issue because we examined only the average frequency of spells over time. In this long duration of observation, these putative clusters might not be detected. However, note that in the relation Observed frequency = a(First recurrence time)^b, the constant a is ~0.44, indicating that the eventual frequency is only half of the expected value based on the first recurrence time. In this long duration of observation, putative clusters might not be detected. To do so would require a prospective, observational trial in which each event was recorded and no changes were made in treatment.

Uses of first recurrence time. The first recurrence time can be used to risk-stratify patients. Given that many patients may have a reduced risk of syncope after assessment, some might consider it reasonable to suggest that patients be followed up without specific therapy and return for reassessment after the first recurrence of syncope. Patients at low risk for frequent recurrent spells would therefore be spared the potential adverse effects and cost of treatment, and patients at high risk would gain a better estimate of their future course. Similarly, patients who do not have a recurrence within a specific follow-up period might be allowed to resume driving, whereas those with early recurrences might be specifically counseled to refrain from driving (13). The first recurrence time can also be used as a study outcome measure, as is done in studies of paroxysmal arrhythmias (14,15). It is simple, validated and does not require that patients continue receiving possibly ineffective therapy for long periods while having recurrent syncopal spells.

Finally, the first recurrence time can be used to provide estimates of event probabilities that are necessary for sample size calculations. The data in Table 1 provide for the enrollment of high risk patients in trials where the outcome measure is the number of syncopal spells within a defined time, and the relations in Figure 3 provide for the enrollment of patients in trials where the outcome measure is the time to first syncopal recurrence.

Study limitations. This study has several limitations. We did not conduct pure natural history study of patients in a drug-free state. Ideally, we would have studied the natural history of patients who received no attempts at specific therapy for syncope. Because recurrent syncopal and presyncopal spells pose significant morbidity, many patients sought and received pharmacologic attempts at therapy. It is possible that the medications altered the eventual temporal behavior of our study cohort. However, the high correlation coefficients and the results of the subgroup analyses suggest the robustness of the relations between interevent intervals and recurrence frequencies.

This report concerns patients with a positive outcome in response to the isoproterenol–head-up tilt table test protocol used in our laboratory. Therefore, we cannot comment on the long-term outcome of patients with a positive outcome in response to passive prolonged head-up tilt testing (16,17) or to tilt testing using one of a variety of other provocative agents, such as nitroglycerin (18), or a different dose of isoproterenol (19–21). These limitations are particularly relevant because the sensitivity and specificity of the various protocols may differ (22,23).

We used syncope, not presyncope, as the outcome measure. However, part of our clinical interaction with patients included teaching the specific physical maneuvers to abort the progression of presyncope to syncope. If successful, this might reduce the risk of syncope without reducing the clinical burden of presyncope.

This study focused on a highly symptomatic, young cohort; half the patients had had >17 historical syncopal spells, and the mean age was 32 years. This was not our explicit intention

because the inclusion criteria specified that patients need only have a positive tilt test result and at least one syncopal spell within a follow-up period lasting at least 2 years after tilt testing. The study cohort otherwise was broadly representative. The patients had a broad age range and presented with a wide range of historical number of syncopal spells and duration of symptoms.

We did not assess the use of a pretest interevent interval as a predictor of eventual frequency in patients who did not undergo tilt table testing. The impact of the tilt test itself on long-term outcome is unknown, and untested patients include those who will have a negative tilt table test. Whether these patients behave similarly is unknown, although we have presented preliminary data indicating that this may be so (24). Hence, our results may not apply to patients without a tilt test.

References

1. Sheldon R, Rose S, Flanagan P, Koshman ML, Killam S. Risk factors for syncope recurrence after a positive tilt table test in patients with syncope. Circulation 1996;93:973–81.
2. Linzer M, Pontinen M, Gold DT, Divine GW, Felder A, Brooks WB. Impairment of physical and psychosocial function in recurrent syncope. J Clin Epidemiol 1991;44:1037–43.
3. Linzer M, Gold DT, Pontinen M, Divine GW, Felder A, Brooks WB. Recurrent syncope as a chronic disease: preliminary validation of a disease-specific measure of functional impairment. J Gen Intern Med 1994;9:181–6.
4. Pritchett ELC, Lee KL. Designing clinical trials for paroxysmal atrial tachycardia and other paroxysmal arrhythmias. J Clin Epidemiol 1988;41: 851–8.
5. Greer SG, Wilkinson WE, McCarthy EA, Pritchett ELC. Random and nonrandom behavior of symptomatic paroxysmal atrial fibrillation. Am J Cardiol 1989;64:339–42.
6. Page RL, Wilkinson WE, Clair WK, McCarthy EA, Pritchett ELC. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. Circulation 1994;89: 224–7.
7. Natale A, Geiger MJ, Maglio C, et al. Recurrence of neurocardiogenic syncope without pharmacologic interventions. Am J Cardiol 1996;77:1001–3.
8. Mitchell LB, Wyse DG, Duff HJ. Programmed electrical stimulation studies of ventricular tachycardia in humans: the role of ventricular functional refractoriness in tachycardia induction. J Am Coll Cardiol 1986;8:567–75.
9. Sheldon RS, Rose S, Flanagan P, Koshman ML, Killam S. Effect of beta blockers on the clinical outcome of patients after a positive isoproterenol-tilt table test. Am J Cardiol 1997;78:536–9.
10. Sheldon RS, Killam S. Methodology of isoproterenol-tilt table testing in patients with syncope. J Am Coll Cardiol 1992;19:773–9.
11. Sheldon R. Evaluation of a single-stage isoproterenol-tilt table test in patients with syncope. J Am Coll Cardiol 1993;22:114–8.
12. Cook DJ, Guyatt GH, Laupacis A, Sackett DL. Rules of evidence and clinical recommendations on the use of antithrombotic agents. Chest 1992; 102:3055–115.
13. Sheldon RS, Koshman ML. Can patients with neuromediated syncope safely drive motor vehicles? Am J Cardiol 1995;75:955–6.
14. Pritchett ELC, McCarthy EA, Wilkinson WE. Propafenone treatment of symptomatic paroxysmal supraventricular arrhythmias: a randomized, placebo-controlled, crossover trial in patients tolerating oral therapy. Ann Intern Med 1991;114:539–44.
15. Anderson JL, Gilbert EM, Alpert BL, et al. Prevention of symptomatic recurrences of paroxysmal atrial fibrillation in patients initially tolerating antiarrhythmic therapy: a multicentre, double-blind, crossover study of flecainide and placebo with transtelephonic monitoring (Flecainide Supraventricular Tachycardia Study Group). Circulation 1989;80:1557–70.
16. Almquist A, Goldenberg IF, Milstein S, et al. Provocation of bradycardia and hypotension by isoproterenol and upright posture in patients with unexplained syncope. N Engl J Med 1989;320:346–51.
17. Fitzpatrick A, Sutton R. Tilting towards a diagnosis in recurrent unexplained syncope. Lancet 1989;1:658–60.
18. Raviele A, Gasparini G, Di Pede F. Nitroglycerine infusion during upright tilt: A new test for the diagnosis of vasovagal syncope. Am Heart J 1994;127:103–11.
19. Morillo CA, Klein GJ, Zandri S, Yee R. Diagnostic accuracy of a low-dose isoproterenol head-up tilt protocol. Am Heart J 1995;129:901–6.
20. Kapoor W, Brant N. Evaluation of syncope by upright tilt testing with isoproterenol: a nonspecific test. Ann Intern Med 1992;116:358–63.
21. Natale A, Akhtar M, Jazayeri M, et al. Provocation of hypotension during head-up tilt testing in subjects with no history of syncope or presyncope. Circulation 1995;92:54–8.
22. Sheldon RS. Tilt table testing in the diagnosis and treatment of syncope. Cardiovasc Rev Rep 1994;15:8–28.
23. Kapoor WN. Diagnostic evaluation of syncope. Am J Med 1991;90:91–106.
24. Sheldon R, Rose S, Koshman M. Clinical outcome of patients with syncope of unknown cause following a negative tilt table test [abstract]. Circulation 1995;92 Suppl I:I–413.